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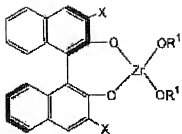
(54) CHIRAL ZIRCONIUM CATALYST AND METHOD FOR SYNTHESIZING
OPTICALLY ACTIVE ANTIALDOL MATERIAL USING THIS CATALYST

(57)Abstract:

PROBLEM TO BE SOLVED: To provide a method for synthesizing an optically active antialdol material by which high antiselectivity and yield can be achieved under milder conditions than by a conventional method.

SOLUTION: This chiral zirconium catalyst is characterized in that it is represented by formula (1): (wherein, X is a halogen atom or a

(1) hydrogen atom and R1 is an alkyl group or an aryl group). The method for synthesizing the optically active antialdol material is to make aldehyde chemically react with a silylenol ether using this catalyst.



CLAIMS

[Claim(s)]

[Claim 1]The following general formula (1);

[Formula 1]

(X in a formula shows a halogen atom or a hydrogen atom, and R¹ shows an alkyl group or an aryl group.) -- chiral zirconium catalyst characterized by what is expressed.

[Claim 2]A synthesizing method of an optical activity anti-aldol object making silyl enol ether react to aldehyde under existence of the chiral zirconium catalyst according to claim 1.

[Claim 3]A synthesizing method of an optical activity anti-aldol object of claim 2 carrying out under existence of alcohol.

 DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention]The invention of this application relates to a chiral zirconium catalyst. Optical activity anti for which the invention of this application used the chiral zirconium catalyst in more detail . It is related with the synthesizing method of an aldol object.

[0002]

[SUBJECT with a Prior art] In the nature, the substance of many including protein etc. is an optically active substance, and making specific physiology activity reveal according to the spacial configuration is known. Therefore, it is thought indispensable to establish a stereoselective synthetic method in the total synthesis of the physiological active substance used as important SUBJECT in the field of medicine, agricultural chemicals, perfume, etc.

[0003]The aldol reaction known as a reaction of ketone and aldehyde which have alpha hydrogen conventionally was considered as the very important reaction in medicine production, and is used until now. And the system using various catalysts is studied and reported as a means of a stereoselective reaction by recent years.

[0004]For example, the reaction (Mukoyama aldol reaction) of the silyl enol ether using Lewis acid and aldehyde is known as an effective method of forming carbon-carbon bonding selectively in organic chemistry.

Tin, boron, titanium, Various compounds using copper etc. as a Lewes acid catalyst. it is reported (Comprehensive Asymmetric Catalysis, 1999, Vol.3, p.998, and Chem. -- Rev., 1999, 99, 1095, Chem. Eur. J. 1998, and 4-1137.) Tetrahedron: Asym., 1998, 9, 357, Angew. Chem. Int. Ed. Engl., 1994, 33, 417.

[0005]These methods have the high stereoselectivity in a reaction, and have been considered to be one of the most efficient reactions in composition of chiral beta-hydroxyketone or an ester derivative. However, there was a problem of needing reaction temperature as low as -78 ** and the severe conditions of perfect non-watery voice, actually.

[0006]The aldol reaction with high syn-selectivity is anti although a large number have so far been studied. - The actual condition is seldom known about the aldol reaction of selectivity. what is reported at present (Tetrahedron Lett., 1992, and 33-1729.) J. there

being problems -- the compound which the yield of output is low and can use in Am. Chem. Soc., 1994, 116, and 4077 is restricted -- and saying that it is practical -- difficulty -- and -- it is -- **

[0007]The invention of this application is [in / it is made in view of the situation as above, conquer the limit of conventional technology, and / the bottom of the usual condition] high anti . Optical activity anti which can obtain selectivity and yield . It is making to provide the synthesizing method of an aldol object into SUBJECT.

[0008]

[Means for Solving the Problem]An invention of this application is the following general formula in the 1st first as what solves above-mentioned SUBJECT (1).;

[0009]

[Formula 2]

[0010]The chiral zirconium catalyst characterized by what is expressed with (X in a formula shows a halogen atom or a hydrogen atom, and R¹ shows an alkyl group or an aryl group) is provided.

[0011]The invention of this application provides the 2nd with the synthesizing method of the optical activity anti-aldol object making silyl enol ether react to aldehyde under existence of the above-mentioned chiral zirconium catalyst.

[0012]Optical activity anti of the above [3rd / the] in the invention of this application furthermore . It provides as that mode that composition of an aldol object is performed under existence of alcohol.

[0013]

[Embodiment of the Invention]As above, the invention of this application uses a new chiral zirconium catalyst, and is high anti about aldehyde and silyl enol ether . Although an aldol reaction is carried out with selectivity, that operation is explained below.

[0014]The chiral zirconium catalyst expressed with said general formula (1) is acquired by mixing Zr(O^tBu)₄, the (R)-3,3'-dibromo-1, and 1'-** 2-naphthol ((R)-3 and 3'-BrBINOL), for example. At this time, Br and R¹ become t-butyl group X in a general formula (1). Of course, X may not be limited to Br, for example, may be halogen atoms, such as I and Cl, or a hydrogen atom. R¹ is not limited to a t-Bu basis, but Methyl, ethyl, n-propyl, Aryl groups, such as alkyl groups, such as i-propyl, n-butyl, sec-butyl, hexyl, cyclopropyl, cyclobutyl, and cyclopentyl, or phenyl, tolyl one, and xylyl, etc. are applied.

[0015]It is high anti by making silyl enol ether react to aldehyde further in the invention of this application using the above-mentioned chiral zirconium catalyst

which is a new substance. - An optical activity aldol object can be acquired with selectivity.

[0016]As aldehyde, they are the following chemical formulas (2).:

R^2CHO (2)

Come out, and it is expressed and R^2 Methyl, ethyl, n-propyl, i-propyl, Aryl groups, such as alkylene groups, such as alkyl groups, such as n-butyl, sec-butyl, hexyl, cyclopropyl, cyclobutyl, and cyclopentyl, ethylene, propylene, butylene, and amylenes, or phenyl, tolyl, and xylyl, are applied. These substituents may have a substituent further, for example, a halogenation phenyl group, p-methoxyphenyl group, benzyl, etc. are illustrated. Of course, R^2 is not limited to the substituent of the more than illustrated here.

[0017]Especially as silylenal, although not limited, they are the following desirable chemical formulas (3).:

[0018]

[Formula 3]

[0019]It comes out and what is expressed is illustrated. At this time, R^3 in formula, R^4 , and R^5 show same or various substituents to another ** respectively. Specifically, it is chosen from an alkyl group and an alkylene group which do not have or have a substituent, an amino group, a cyano group, a nitro group, a thiol group, a sulfone group, a carbonyl group, a carboxyl group, an alkoxy carbonyl group, or a hydrogen atom. For example, a methyl group, an ethyl group, a propyl group, a phenyl group, benzyl, a methoxy group, a phenoxy group, etc. are illustrated. Of course, R^3 - R^5 are not limited to these substituents, but can apply a thing of various structures as silyl enol ether.

[0020]Conditions in particular of a reaction are not limited, for example, water and various organic solvents are taken into consideration as a reactional solvent. Preferably, toluene is used. At this time, it becomes dispersion liquid. Especially reaction temperature can be suitably changed according to a solvent or a starting material, although not limited. Preferably, it is -10-50 **. Although not limited, in being too low, an effect does not show up easily, and especially concentration of a catalyst to add is anti. - An alternative reaction is hard coming to go on, and an effect does not become large any more above a certain fixed concentration. Therefore, as catalyst concentration, 0.1-100-mol the thing to consider as % is preferred, and may be 1-20-mol % more preferably.

[0021]It is preferred to add alcohol in the system of reaction in an aldol reaction of an invention of this application. By addition of alcohol, alcohol can act as a proton source

of release, a mono- trimethylsilylation BINOL derivative generated as an intermediate product can be transformed to a BINOL derivative, and yield and selectivity can be raised. Although various things are applicable as a kind of alcohol, the univalent 1st class alcohol of ethanol, methanol, propanol, butanol, etc. is used preferably. Of course, they may be alcohol other than this, for example, diol, triol, etc.

[0022]Although not limited especially as a quantity of alcohol to add, since a reaction may be checked on the contrary if not much large, 1-100-mol the thing to consider as % is preferred.

[0023]Hereafter, an example is shown and an invention of this application is explained in more detail. This invention is not limited to these examples.

[0024]

[Example]In the following reference examples and examples, the ^1H and ^{13}C NMR spectrum was measured by each by using CDCl_3 as a solvent, unless it mentioned specially using JEOL JNM-LA300, JNM-LA400, or JNM-LA500. As ^1H NMR, the tetramethylsilane (TMS) was made into the internal standard ($\delta=0$), and by ^{13}C NMR, unless it was mentioned specially as CD_2Cl_2 use, CDCl_3 was made into the internal standard ($\delta=77.0$).

[0025]High performance chromatography (HPLC) was performed using SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD10-A (UV detector), and a SHIMADZU C-R6A chromatopack.

[0026]Column chromatography was carried out using silica gel 60 (made by Merck Co.), and thin layer chromatography was performed using WakogelB-5F.

[0027]The dichloromethane used for the experiment was distilled under CaH_2 next under P_2O_5 , and after drying under MS 4A, it was used. Toluene was used after drying under MS 4A. It distilled under Mg and dried under MS 4A, and alcohol carried out argon enclosure further and was saved. Distillation or sublimation refined aldehyde before use.

[0028]All the silyl enol ether was compounded in accordance with the method (J. Org.Chem., 1969, 34, 2324) of House. The 3 and 3'-BINOL derivative was compounded in accordance with the method (Tetrahedron Lett., 1992, 33, 2253) of Sniekus.

In the preparation (for NMR measurement) room temperature of a <reference example> chiral zirconium catalyst, (R)-3 and 3'-diiodo 1 and 1'-** 2-naphthol (3 and 3'-IBINOL) (44 mg, 0.08 mmol) are added to CD_2Cl_2 (0.5 ml), After considering it as dispersion liquid, the CD_2Cl_2 (0.50 ml) solution of $\text{Zr}(\text{O}^i\text{Bu})_4$ (30.6 mg, 0.04 mmol) was added, and propanol (24.1 mg, 0.4 mmol) was added further. It introduced into the sample tubing for NMR, after stirring this solution for 60 minutes.

[0029]NMR measurement was performed by making CD_2Cl_2 (^1H NMR δ = 5.32 ppm and ^{13}C NMR δ = 53.1 ppm) into a standard. A result is shown in Table 1.

[0030]

[Table 1]

[0031]The acquired chiral zirconium catalyst was a (NAFTA range ORATO)-dialkoxo zirconium, and X was [I and R^1] a compound of $t\text{Bu}$ in the general formula (1).

< example 1> anti- According to the influence chemical formula [A] of the catalyst in an alternative dissymmetry aldol reaction, and an alcoholic kind, the aldol reaction of benzaldehyde (2a) and a silyleno rate (3a) was performed. The compound and alcohol which show a catalyst in the following chemical formulas (1 a-d) were chosen from n-propanol (PrOH), i-propanol (iPrOH), n-butanol (BuOH), and t-butanol (tBuOH).

[0032]

[Formula 4]

[0033]

[Formula 5]

[0034]The yield and optical activity (ee%) of output which were acquired are shown in Table 2.

[0035]

[Table 2]

[0036]From this, it was shown that the yield in a reaction and the optical purity of output improve by addition of propanol. It was checked rather than $t\text{BuOH}$ that PrOH shows a high effect to improvement in yield and optical purity rather than iPrOH in BuOH.

<Example> 2 (R)-3,3'-diiodo 1,1'-**'- 2-naphthol (0.044 mmol) is added in toluene (0.25 ml). After considering it as suspension, the toluene (0.50 ml) solution of $\text{Zr}(\text{O}^t\text{Bu})_4$ (0.04mmol) was added at the room temperature, and it mixed. The obtained mixed liquor was stirred at the room temperature for 30 minutes, and the toluene (1.0 ml) solution of n-propanol (0.20 mmol) was added. This mixed liquor was stirred for 30 more minutes, and it cooled at 0 **.

[0037]After adding benzaldehyde (0.80 mmol) and the toluene (0.50 ml) solution of the silyleno rate (3b) (0.96 mmol) and stirring for 18 hours, saturation NaHCO_3 was added and the reaction was suspended.

[0038]1 time processing of the crude things obtained by dichloromethane's washing a water layer and separating liquids was carried out by $\text{THF} \cdot 1\text{N HCl}$ (20:1) at 0 **, and a little silyl ghosts were hydronalium-ized. Separation refinement of the obtained rough product was carried out on silica gel.

[0039]The acquired output was identified by NMR. Identified results are shown in Table 3.

[0040]

[Table 3]

[0041]The yield of output and optical purity (ee%) were shown in Table 4.

By the same method as <Examples 3-12> example 2, each aldehyde of Table 3 and the aldol reaction of the silyleno rate were performed.

[0042]It asked for the yield of the acquired output, a syn/anti ratio, and optical purity (ee%), and Examples 2-12 were shown in Table 4.

[0043]

[Table 4]

[0044]The structure of each output (4a-4k) was checked by NMR. Identified results are shown in Tables 5-14.

[0045]

[Table 5]

[0046]

[Table 6]

[0047]

[Table 7]

[0048]

[Table 8]

[0049]

[Table 9]

[0050]

[Table 10]

[0051]

[Table 11]

[0052]

[Table 12]

[0053]

[Table 13]

[0054]

[Table 14]

[0055]As mentioned above, it is anti by using the chiral zirconium catalyst of an invention of this application. It was shown that a dissymmetry aldol reaction advances selectively. It was checked that this reaction is applied to the reaction of not

only a specific starting material but various aldehyde and a silyleno rate.

[0056]

[Effect of the Invention] A new chiral zirconium catalyst was provided by the invention of this application as explained in detail above. And it is anti high under conditions quieter than the conventional method by using this chiral zirconium catalyst. - Selectivity and optical activity anti which can attain yield - It becomes compoundable [an aldol object]. In the synthesizing method of this optical activity anti- aldol object, the compound of not only the limited compound but many can apply as a starting material.

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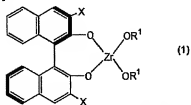
(54) 【発明の名称】 キラルジルコニウム触媒とそれを用いた光学活性 anti-1-アルドール体合成方法

(57) 【要約】

【課題】 従来方法よりも穏やかな条件下で、高いanti-選択性と収率を達成できる、光学活性anti-1-アルドール体の合成方法を提供する。

【解決手段】 次の一般式(1)：

【化6】



(式中のXは、ハロゲン原子または水素原子を示し、R¹は、アルキル基、またはアリール基を示す。)で表されることを特徴とするキラルジルコニウム触媒と、それを用いてアルデヒドと、シリルエノールエーテルを反応させる光学活性anti-1-アルドール体の合成方法。